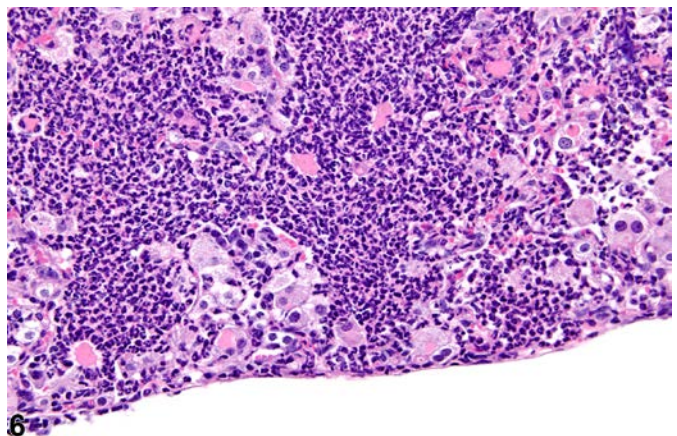
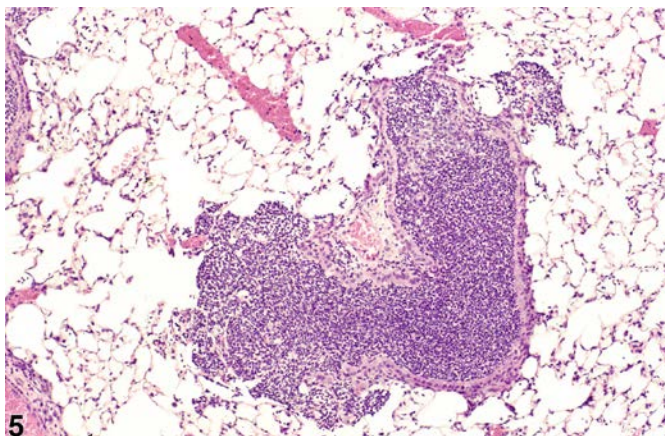
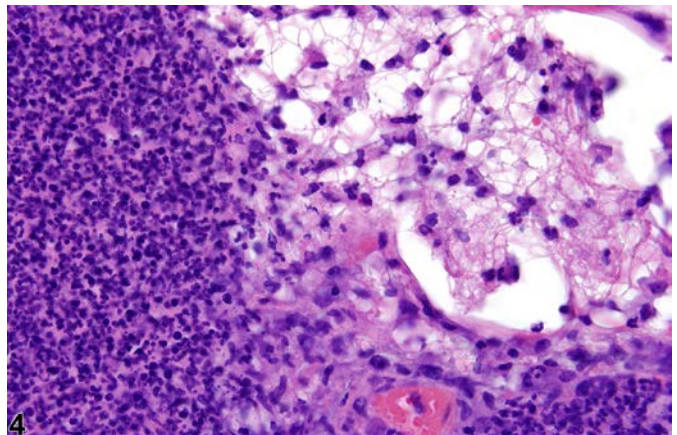
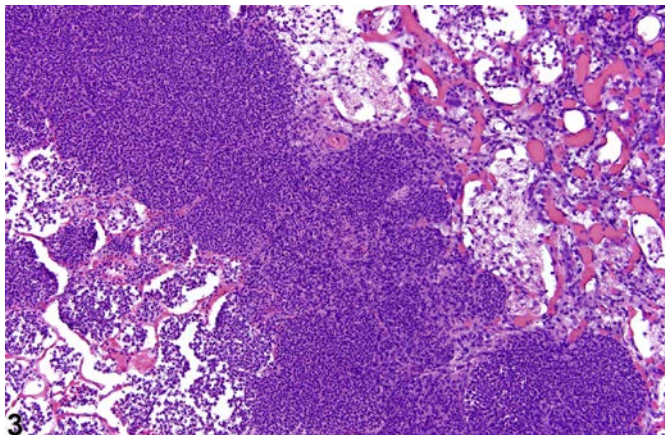
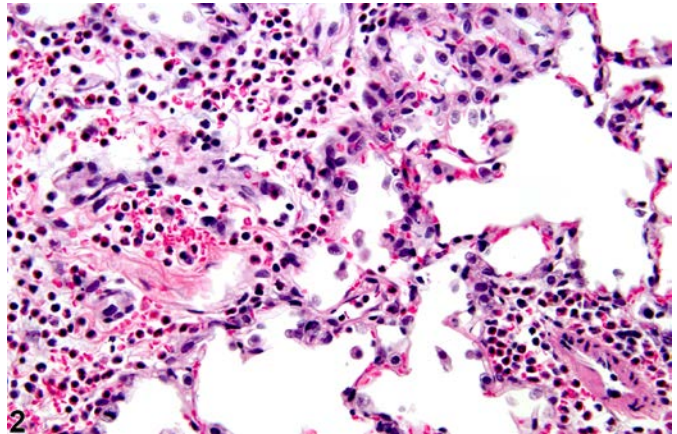
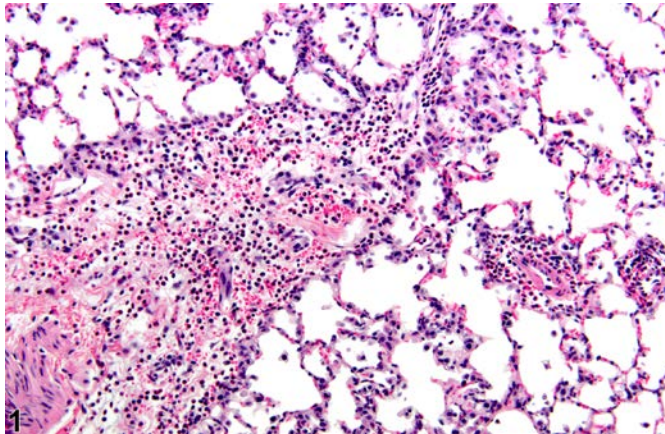
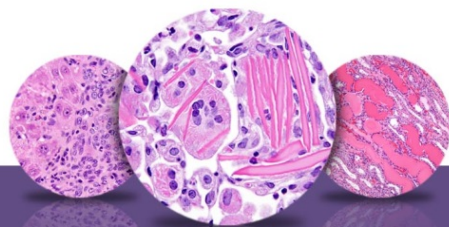


NTP Nonneoplastic Lesion Atlas

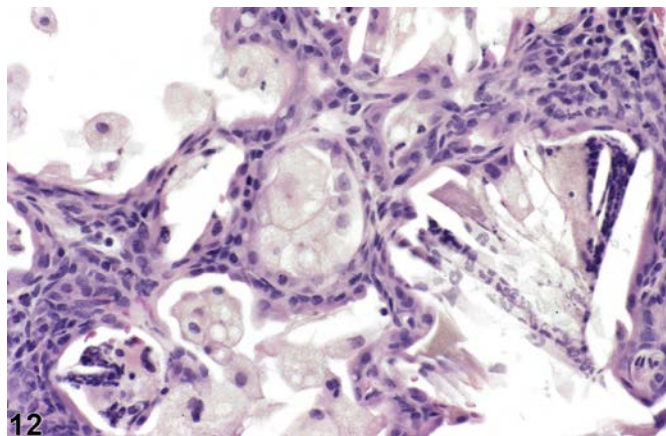
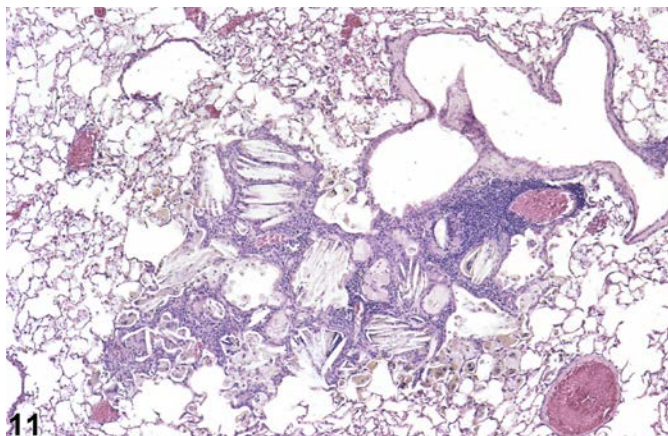
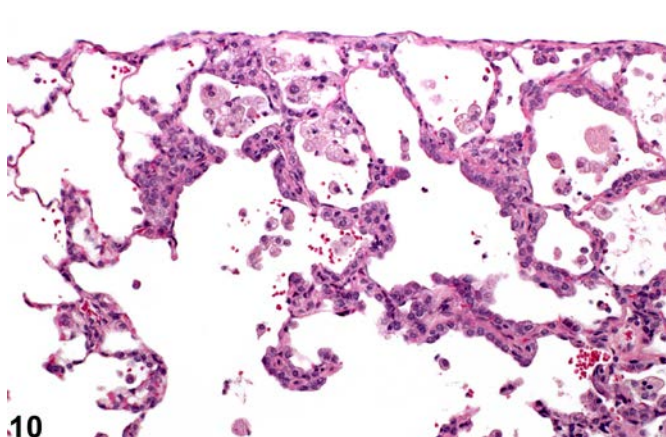
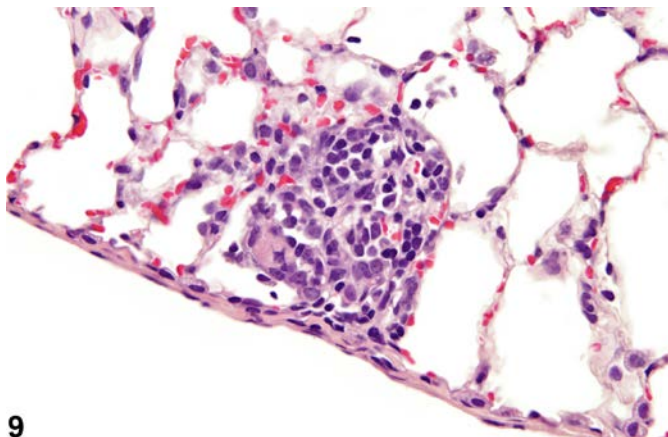
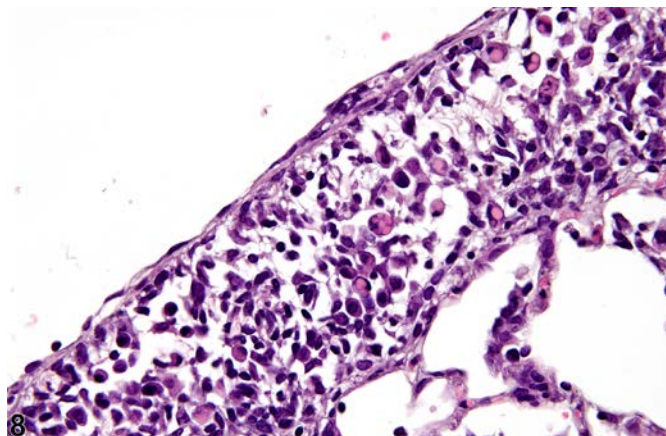
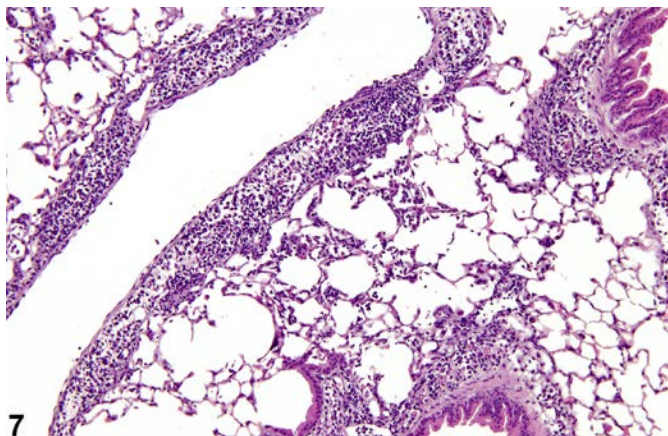
Lung – Inflammation

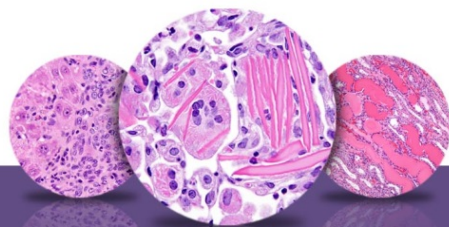




NTP Nonneoplastic Lesion Atlas

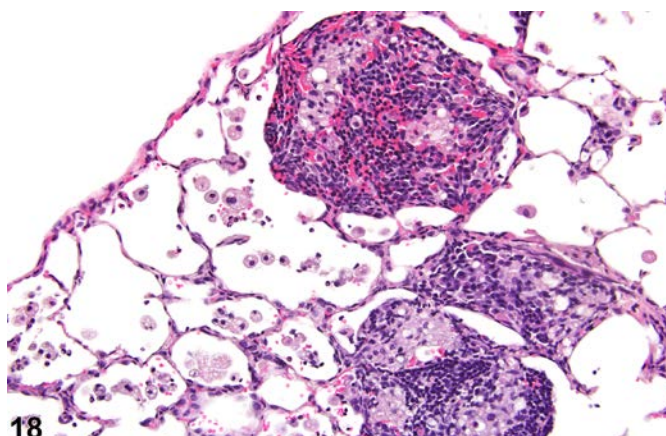
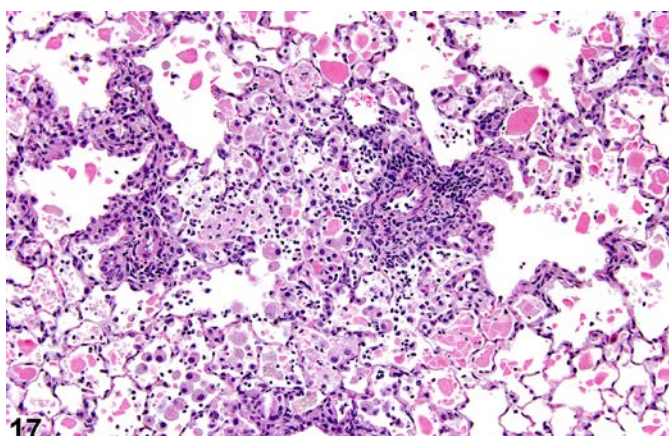
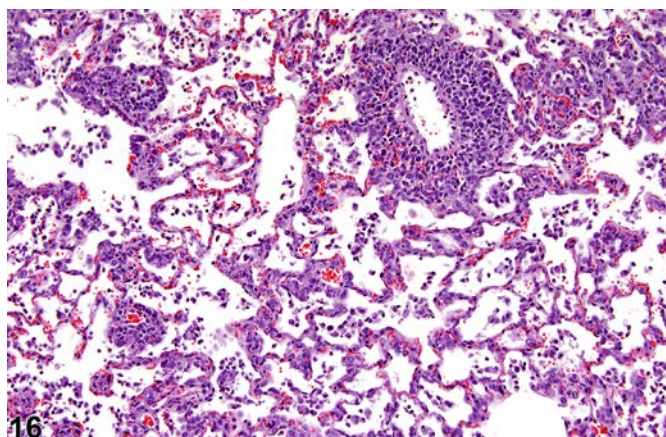
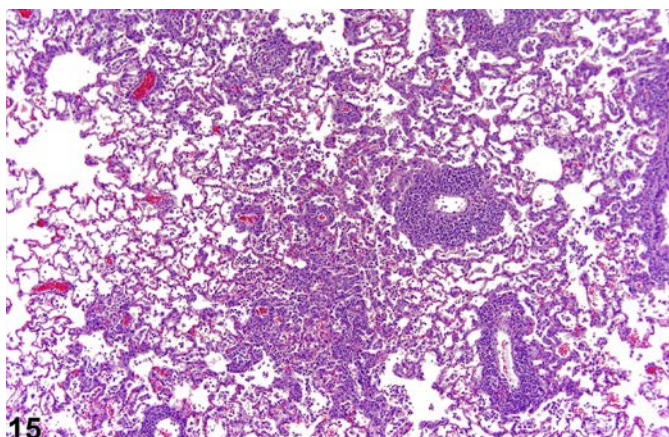
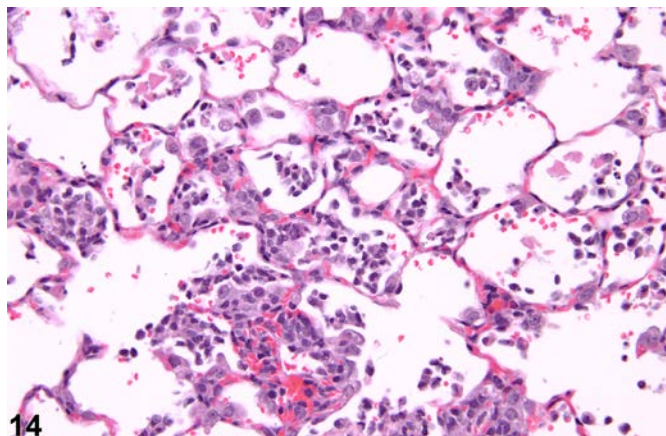
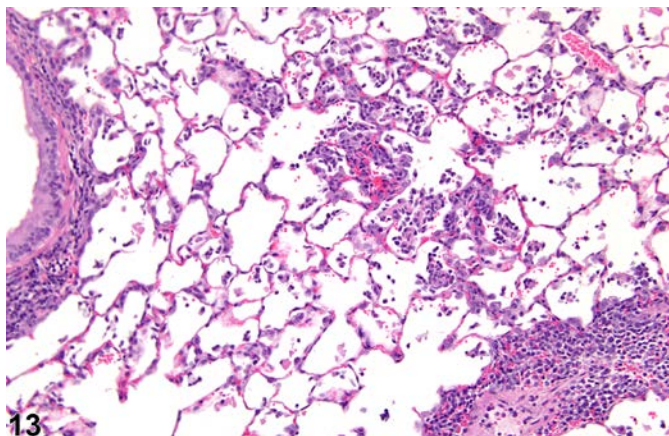
Lung – Inflammation

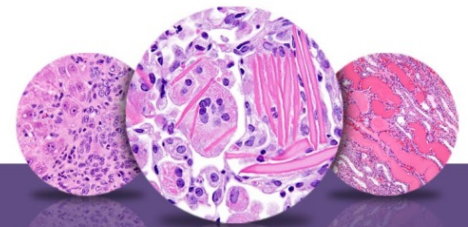




NTP Nonneoplastic Lesion Atlas

Lung – Inflammation





NTP Nonneoplastic Lesion Atlas

Lung – Inflammation

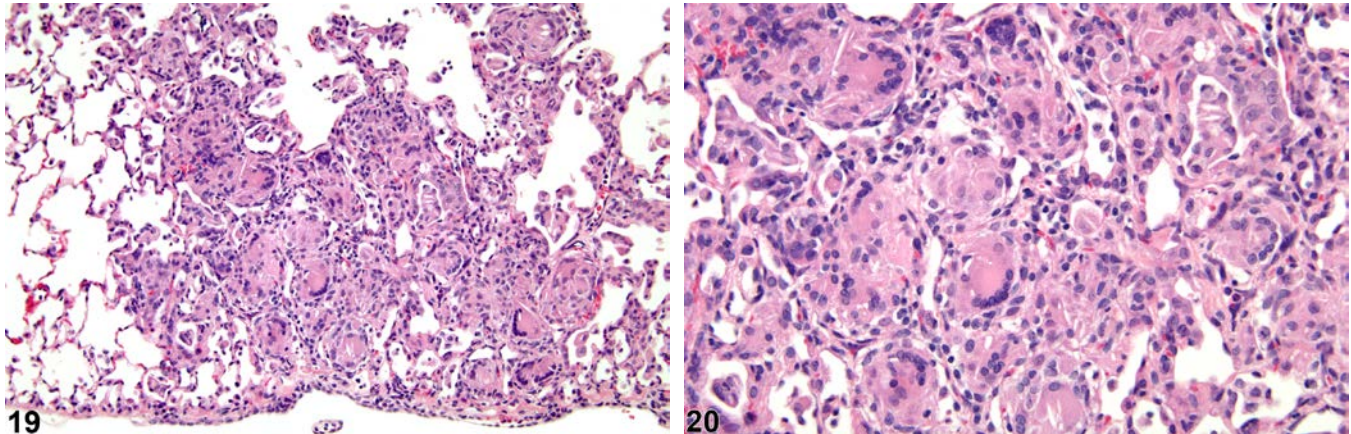
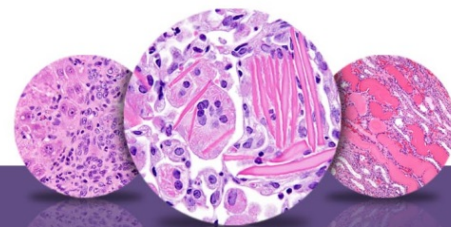


Figure Legend: **Figure 1** Lung - Inflammation, Acute in a male Wistar Han rat from a subchronic study. The majority of the inflammatory cells are neutrophils; there is also a small amount of hemorrhage. **Figure 2** Lung - Inflammation, Acute in a male Wistar Han rat from a subchronic study (higher magnification of Figure 1). The majority of the inflammatory cells are neutrophils, but there are also mononuclear cells, including alveolar macrophages. **Figure 3** Lung - Inflammation, Suppurative in a male Wistar Han rat from a chronic study. Large numbers of degenerate neutrophils fill and replace alveoli. **Figure 4** Lung - Inflammation, Suppurative in a male Wistar Han rat from a chronic study (higher magnification of Figure 3). Abundant necrotic debris is admixed with the degenerate neutrophils. **Figure 5** Lung, Bronchiole - Inflammation, Suppurative in a male B6C3F1/N mouse from a chronic study. Degenerate neutrophils fill the bronchiole. **Figure 6** Lung - Inflammation, Suppurative in a female B6C3F1/N mouse from a chronic study. There are numerous large, foamy, activated alveolar macrophages amid the degenerate neutrophils. **Figure 7** Lung - Inflammation, Chronic in a female B6C3F1/N mouse from a chronic study. The mononuclear inflammatory cells are largely perivascular, peribronchiolar, and subpleural. **Figure 8** Lung - Inflammation, Chronic in a female B6C3F1/N mouse from a chronic study (higher magnification of Figure 7). Mott cells are visible amid the lymphocytes and plasma cells in the subpleural region. **Figure 9** Lung - Inflammation, Chronic in a male F344/N rat from a subchronic study. These focal, subpleural lesions are a common background finding. **Figure 10** Lung - Inflammation, Chronic in a male F344/N rat from a subchronic study. This is a slightly more severe example of the common background lesion shown in Figure 9, with thickening of the alveolar septa. **Figure 11** Lung - Inflammation, Chronic in a female B6C3F1/N mouse from a chronic study. Numerous

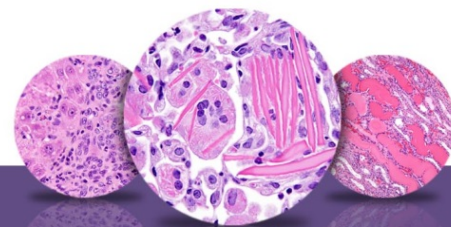


NTP Nonneoplastic Lesion Atlas

Lung – Inflammation

cholesterol clefts and pigmented macrophages are present in this inflammatory lesion. **Figure 12** Lung - Inflammation, Chronic in a female B6C3F1/N mouse from a chronic study (higher magnification of Figure 11). The macrophages are large, foamy, and activated. **Figure 13** Lung - Inflammation, Chronic active in a male F344/N rat from a subchronic study. There is a mixture of lymphocytes, macrophages, and neutrophils. **Figure 14** Lung - Inflammation, Chronic active in a male F344/N rat from a subchronic study (higher magnification of Figure 13). There is a mixture of lymphocytes, macrophages, and neutrophils, with a small amount of alveolar hemorrhage. **Figure 15** Lung - Inflammation, Chronic active in a male F344/NTac rat from a subchronic study. The perivascular and interstitial inflammation in this control rat is consistent with *Pneumocystis carinii* infection (formerly rat respiratory virus). **Figure 16** Lung - Inflammation, Chronic active in a male F344/NTAC rat from a subchronic study (higher magnification of Figure 15). The lesion is consistent with *Pneumocystis carinii* infection (formerly rat respiratory virus). **Figure 17** Lung - Inflammation, Chronic active in a male B6C3F1/N mouse from a subchronic study. There is a mixture of inflammatory cell types, including neutrophils, and alveolar proteinosis. **Figure 18** Lung - Inflammation, Granulomatous in a male Wistar Han rat from a chronic study. Clusters of large, foamy macrophages are surrounded by mononuclear cells. **Figure 19** Lung - Inflammation, Granulomatous in a female F344/NTAC rat from a subchronic study. There are numerous multinucleated giant cells in this lesion. **Figure 20** Lung - Inflammation, Granulomatous from a female F344/NTac rat in a subchronic study (higher magnification of Figure 19). The multinucleated giant cells are of the Langhans type.

Comment: Inflammation of the lungs is one of the most common lesions seen in inhalation studies. In NTP studies, there are five standard categories of inflammation: acute, suppurative, chronic, chronic active, and granulomatous. In *acute inflammation* (Figure 1 and Figure 2), the predominant infiltrating cell is the neutrophil, though fewer macrophages and lymphocytes may also be present. There may also be evidence of edema or hyperemia. The neutrophil is also the predominant infiltrating cell type in *suppurative inflammation* (Figure 3, Figure 4, Figure 5, and Figure 6), but they are aggregated, and many of them are degenerate (suppurative exudate). Cell debris, from both the resident cell populations and infiltrating leukocytes, and proteinaceous fluid containing fibrin, fewer macrophages, occasional lymphocytes or plasma cells, and, possibly, an infectious agent may also be present within the exudate. Grossly, these lesions would be characterized by the presence of pus. The tissue surrounding the



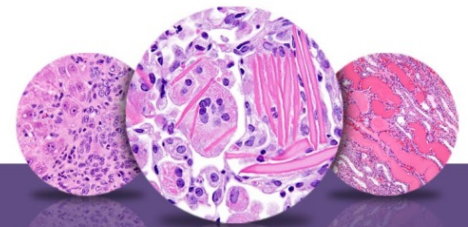
NTP Nonneoplastic Lesion Atlas

Lung – Inflammation

exudate may contain fibroblasts, fibrous connective tissue, and mixed inflammatory cells, depending on the chronicity of the lesion. Lymphocytes predominate in *chronic inflammation* (Figure 7, Figure 8, Figure 9, Figure 10, Figure 11, and Figure 12). Lymphocytes also predominate in *chronic active inflammation* (Figure 13, Figure 14, Figure 15, Figure 16, and Figure 17), but there are also a significant number of neutrophils. Both lesions may contain macrophages. Granulomatous inflammation (Figure 18, Figure 19, and Figure 20) is another form of chronic inflammation, but this diagnosis requires the presence of a significant number of aggregated, large, activated macrophages, epithelioid macrophages, or multinucleated giant cells. In all forms of inflammation, there may also be edema, hemorrhage, fibrin, proteinosis, degeneration, or necrosis. Inflammation is differentiated from cellular infiltrates by the presence of other changes, such as edema, hemorrhage, degeneration, necrosis, or other evidence of tissue damage.

A test agent may stimulate epithelial cells and resident macrophages to secrete cytokines, thus inducing an inflammatory response. Alternatively, a test agent may cause tissue damage, which secondarily results in inflammation. Several compartments within the lung may be inflamed, including the airways (bronchi and bronchioles), the alveoli or alveolar septa (interstitium), the terminal bronchiole/alveolar duct region (acinar region), perivascular areas, and the pleura. Occasionally, focal, minimal inflammation in the lung is seen as a background lesion in mice and rats (Figure 9 and Figure 10), particularly in the subpleural region. Small aggregates of alveolar histiocytes can also be seen (see Lung – Infiltration cellular, Histiocyte) as a background lesion and must be differentiated from inflammation. Inflammation can also be caused by a number of infectious agents, but these are rare under current husbandry practices. Systemic bacterial infections affecting the pulmonary interstitium via the bloodstream often produce a suppurative alveolitis, whereas viral infections tend to induce suppurative or mononuclear perivascular inflammation. Inflammation can also be associated with pulmonary neoplasms.

Recommendation: Whenever present, Lung - Inflammation should be diagnosed and assigned a severity grade. A site modifier (e.g., perivascular, interstitial, bronchial, bronchiolar, pleural, or subpleural) should be included in the diagnosis to indicate the location of the lesion. Also, the type of inflammation (e.g., acute, chronic) should be included in the diagnosis as a modifier. If the inflammation



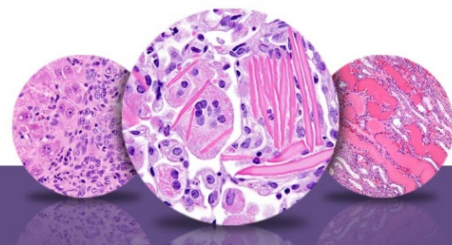
NTP Nonneoplastic Lesion Atlas

Lung – Inflammation

affects more than one site, the site modifier may be omitted and the affected locations identified in the pathology narrative. The term “inflammation” should be used when the inflammatory cells are accompanied by other changes indicative of inflammation, such as vascular changes (which may result in hemorrhage or edema), necrosis or degeneration of cells, or disruption of the normal architecture. Lesions that are considered part of the inflammatory process, such as edema and hemorrhage, need not be diagnosed separately unless warranted by severity but should be described in the narrative. Necrosis or degeneration of cells may be primary, inciting an inflammatory response, or it may be secondary to the inflammation. Therefore, it can be very difficult to determine which lesion (necrosis or inflammation) is primary and which is secondary. The pathologist should use his or her judgment in determining whether to diagnose these lesions separately or to combine these related lesions into a single diagnosis. If they are combined into a single diagnosis, all components of the lesions should be thoroughly described in the narrative. A small, focal accumulation of inflammatory cells with no other evidence of inflammation (e.g., edema, hemorrhage, cell swelling, degeneration, or necrosis, alveolar septal thickening, fibrin deposition), should be diagnosed as “infiltration cellular” rather than inflammation. When present as a secondary finding to a neoplasm, the inflammation need not be diagnosed separately but should be described in the pathology narrative.

References:

- Boorman GA, Eustis SL. 1990. Lung. In: Pathology of the Fischer Rat: Reference and Atlas (Boorman GA, Eustis SL, Elwell MR, Montgomery CA, MacKenzie WF, eds). Academic Press, San Diego, CA, 339-367.
- Dixon D, Herbert RA, Sills RC, Boorman GA. 1999. Lungs, pleura, and mediastinum. In: Pathology of the Mouse: Reference and Atlas (Maronpot RR, Boorman GA, Gaul BW, eds). Cache River Press, Vienna, IL, 293-332.
- Dungworth DL, Ernst H, Nolte T, Mohr U. 1992. Nonneoplastic lesions in the lungs. In: Pathobiology of the Aging Rat (Mohr U, Dungworth DL, Capen CC, eds). ILSI Press, Washington, DC, 143-160.
- Plopper CG, Dungworth DL. 197. Structure, function, cell injury and cell renewal of bronchiolar and alveolar epithelium. In: Lung Carcinomas (McDowell EM, ed). Churchill Livingstone, Edinburgh, 94-128.
- Renne R, Brix A, Harkema J, Herbert R, Kittel K, Lewis D, March T, Nagano K, Pino M, Rittinghausen S, Rosenbruch M, Tellier P, Wohrmann T. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. Toxicol Pathol 37(suppl):5S-73S.
Abstract: <http://www.ncbi.nlm.nih.gov/pubmed/20032296>



NTP Nonneoplastic Lesion Atlas

Lung – Inflammation

Authors:

Mark F. Cesta, DVM, PhD, DACVP
Staff Scientist/NTP Pathologist
NTP Pathology Group
National Toxicology Program
National Institute of Environmental Health Sciences
Research Triangle Park, NC

Darlene Dixon, DVM, PhD, DACVP
Group Leader
Molecular Pathogenesis Group
National Toxicology Program
National Institute of Environmental Health Sciences
Research Triangle Park, NC

Ronald A. Herbert, DVM, PhD
Group Leader/NTP Pathologist
Pathology Support Group
National Toxicology Program
National Institute of Environmental Health Sciences
Research Triangle Park, NC

Lauren M. Staska, DVM, PhD, DACVP
Senior Pathologist
WIL Research
Hillsborough, NC